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Background: Clinical guidelines recommend immediate initiation of combined antiretroviral therapy for all HIV-positive individuals. However, those guidelines are based on trials of relatively young participants.

Methods: We included HIV-positive antiretroviral therapy–naive, AIDS-free individuals aged 50–70 years after 2004 in the HIV-CAUSAL Collaboration. We used the parametric g-formula to estimate the 5-year risk of all-cause and non-AIDS mortality under (1) immediate initiation at baseline and initiation at CD4 count, (2) <500 cells/mm^3, and (3) <350 cells/mm^3. Results were presented separately for the general HIV population and for a US Veterans cohort with high mortality.

Results: The study included 9596 individuals (28% US Veterans) with median (interquantile range) age of 55 (52–60) years and CD4 count of 336 (182–513) at baseline. The 5-year risk of all-cause mortality was 0.40% (95% confidence interval (CI): 0.10 to 0.71) lower for the general HIV population and 1.61% (95% CI: 0.79 to 2.67) lower for US Veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3. The 5-year risk of non-AIDS mortality was 0.17% (95% CI: −0.07 to 0.43) lower for the general HIV population and 1% (95% CI: 0.31 to 2.00) lower for US Veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3.

Conclusions: Immediate initiation seems to reduce all-cause and non-AIDS mortality in patients aged 50–70 years.

Key Words: aging, when to start, antiretroviral treatment, CD4 cell count, causal inference, parametric g-formula, comparative effectiveness

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INTRODUCTION

Two randomized clinical trials have shown that combined antiretroviral therapy (ART) initiation at high CD4 counts reduces the risk of serious AIDS and non-AIDS events and death in HIV-positive individuals.[1,2] As a result, clinical guidelines have been updated to recommend ART initiation in all HIV-positive individuals regardless of their CD4 cell count.[3–5] However, these trials comprised relatively young participants (median age 36 years) and the number of deaths was too small to examine effects on mortality. Thus, estimates of the impact of the new recommendations on mortality among older HIV-positive individuals, whose prognosis may be different, are currently lacking.

The number of patients diagnosed with HIV at older age has increased over time.[6] Currently, between 12% and 18% of newly diagnosed HIV-positive individuals are older than 50 years in high-income countries.[7,8] Compared with younger HIV-positive patients, those who enter HIV care at older age are often diagnosed with late or advanced HIV disease,[6] have a diminished immunological response to treatment,[9–11] and are therefore at higher risk of progressing to AIDS or death. The clinical management of these patients is further complicated by a higher prevalence of comorbidities, including hyperlipidemia, cardiovascular disease, cancer, and diabetes.[12] The benefits of immediate ART initiation might be partially or totally offset by polypharmacy, ie, taking a large number of different medicines,[13] that can make adherence to ART more difficult and can increase the risk of drug toxicities and drug interactions.[14]

It is therefore important to quantify the impact of immediate ART initiation in patients who enter into HIV care at older age. Here we estimate the 5-year risk of all-cause mortality and non-AIDS mortality among ART-naive, AIDS-free individuals aged between 50 and 70 years using data from the HIV-CAUSAL Collaboration of HIV cohorts from Europe and the Americas. More specifically, we estimated and compared the mortality risks if all participants had started ART (1) immediately, (2) when their CD4 count dropped below 500 cells/mm,^{3} and (3) when their CD4 count dropped below 350 cells/mm.^{3} We present the results separately for HIV-positive patients from the general population and for US Veterans with high mortality.

METHODS

Selection of Patients

We included individuals aged between 50 and 70 years, who had at least 1 CD4 cell count and 1 HIV-RNA measured within 3 months of each other, whereas ART-naive and AIDS-free after December 31, 2004. Baseline was defined as the earliest of the date when all the inclusion criteria were met. Individuals older than 70 years at baseline were rare in our cohorts and were not included because their clinical management might be different due to a higher burden of comorbidities. We considered 2 populations with different background mortality: HIV-positive patients from the general population and US Veterans known to have higher mortality.[15] Individuals from the general HIV population were enrolled in the following cohorts: AMACS (Greece), ANRS CO3 Aquitaine, French Hospital Database, PRIMO, SEROCO (France), ATHENA (the Netherlands), CoRIS, GEMES, PISCIS (Spain), IPEC (Brazil), Southern Alberta Clinic Cohort (Canada), Swiss HIV Cohort study (Switzerland), UK CHIC, and the UK Register of Seroconverters (United Kingdom). The population of US Veterans included individuals from the Veterans Aging Cohort Study (US).

ART Initiation Strategies

ART was defined as a combination of antiretroviral drugs including at least 2 nucleoside reverse transcriptase inhibitors plus either 1 or more protease inhibitors, 1 nonnucleoside reverse transcriptase inhibitor, 1 entry/fusion inhibitor, or 1 integrase inhibitor.

For each population, we estimated the 5-year risk of all-cause mortality and non-AIDS mortality if all participants had started ART within 3 months of baseline (immediate ART initiation). We compared these estimates with those estimated under ART initiation within 3 months of AIDS diagnosis or CD4 count (1) <500 and (2) <350 cells/mm^3, the ART initiation strategies recommended in different settings before the changes in guidelines. We did not account for episodes of ART discontinuation and we assumed that once ART was started, patterns of treatment discontinuation were the same as in the observed data for each of the 2 populations.

Follow-up

Follow-up started at baseline and ended at the earliest of death, 12 months after the most recent laboratory measurement,

cohort-specific administrative censoring, date of pregnancy when known, 5 years after baseline, or the date a patient initiated ART with a combination other than our definition of ART.

Outcomes

The outcomes, which were analyzed separately, were all-cause mortality and non-AIDS mortality up to 5 years after baseline. For each ART initiation strategy and outcome, we estimated the 5-year risk and risk difference. Non-AIDS mortality was defined as any known cause of death other than AIDS-defining conditions.[16] Cause of death was based on the International Classification of Diseases 10th Revision (ICD-10) and formatted according to CODE (http://www.hicdep.org/). Two cohorts, UK CHIC and IPEC, did not provide data on cause of death and were excluded from the non-AIDS mortality analyses. For all cohorts, death ascertainment and cause of death were based on hospital records and cross-matching with national and local registries.[15]

Statistical Methods

Our estimates had to be adjusted for the time-dependent confounders CD4 cell count, HIV-RNA level and AIDS, as well as for confounders measured at baseline. Because standard statistical methods cannot appropriately adjust for time-dependent confounders affected by previous treatment,[17,18] we applied the parametric g-formula to obtain adjusted estimates for each treatment strategy under the assumptions of no residual confounding, no measurement error, and no model misspecification.[19]

The parametric g-formula is a generalization of standardization for time-varying treatments and confounders.[17,20] The parametric g-formula is used to estimate the risk of mortality that would have been observed if all patients in the study had perfectly complied with a particular treatment initiation strategy and none had been lost to follow-up. The estimation procedure for the HIV-CAUSAL Collaboration has been described elsewhere.[21] Briefly, the procedure has 2 steps. First, parametric regression models are used to estimate the joint distribution of the outcome, treatment and time-varying covariates conditional on previous treatment, and covariate history. Second, a Monte Carlo simulation using the above estimates is run to simulate the distribution of the postbaseline outcomes and time-varying covariates separately under each ART initiation strategy.

For the first step, we fit separate logistic regression models for time-varying indicators for the outcome event, AIDS, ART initiation, measurement of CD4 cell count, measurement of HIV-RNA, and linear regression models for CD4 cell count and HIV-RNA on the natural logarithm scale. All regression models included as covariates the most recent value of these time-varying variables, time since last CD4 count and HIV-RNA measurements, and the following baseline variables: CD4 cell count ($<$100, 100–199, 200–349, 350–499, $\geq$500 cells/mm^3), HIV-RNA level ($<$10000, 10,000–100000, $>$100000 copies/mL), age ($<$60, $\geq$60 years), sex, mode of acquisition (heterosexual, homo/bisexual, injecting drug users, or other/unknown), calendar year (2005–2009, 2010–2015), geographical origin (Western countries, sub-Saharan Africa, other, unknown), and cohort. All models also included an interaction term for number of months since ART initiation.

In the analyses where the outcome was non-AIDS mortality, AIDS mortality and mortality due to unknown cause were treated as competing events. The g-formula estimates of risk in the presence of competing risks should be interpreted as an extension of the sub-distribution cumulative incidence function to the setting of time-varying treatments and confounders.[20]

As in all regression-based methods, the parametric g-formula relies on correct model specification. To explore the validity of our parametric assumptions, we compared the observed means of the outcome and time-varying covariates with those predicted by our models. We used a nonparametric bootstrap procedure based on 500 samples to obtain percentile-based 95% confidence intervals (CIs). All analyses were conducted with the publicly available SAS macro GFORMULA (http://www.hsph.harvard.edu/causal/software/).

Sensitivity Analyses

Because our main analyses included all ART-naive patients regardless of CD4 count at baseline in a sensitivity analysis, we restricted to the subset of individuals in the general HIV population with a CD4 count $\geq$500 cells/mm^3 at baseline. This sensitivity analysis was conducted only in the general HIV population because there were not enough patients and death cases to achieve good model fit in the US Veterans.

Because a nonnegligible proportion of death events had unknown cause of death, as a sensitivity analysis we estimated the risks, risk difference, and risk ratio of non-AIDS mortality assuming that all deaths due to unknown cause were non-AIDS related. This extreme case scenario is unrealistic in practice, but provides an illustration of how sensitive the analyses may be to assumptions regarding the missing data on cause-specific mortality.

RESULTS

Table 1 shows the baseline characteristics of the 9599 eligible individuals, of whom 2672 (28%) were US Veterans. Patients were predominantly males and started follow-up before 2010. The median (interquartile range) age at baseline was 55 years (52–59) in the general HIV population and 56 years (53–60) in US Veterans. The median (interquartile range) CD4 count at baseline was 354 cells/mm^3 (203–530) in the general HIV population and 284 cells/mm^3 (128–471) in US Veterans (Supplemental Digital Content Table 1, http://links.lww.com/QAI/B65).

During a follow-up of 31,989 person years, 7247 individuals initiated ART, 295 individuals died in the general HIV population, and 339 died in the US Veterans cohort. In the general population, there were 124 (55%) non-AIDS deaths, 47 (21%) AIDS deaths, and 54 (24%) deaths with unknown cause. The most common non-AIDS causes of death were non-AIDS cancer (70 events) and cardiovascular disease (21 events). In US Veterans, there were 136 (40%) non-AIDS deaths, 157 (47%) AIDS deaths, and 46 (14%) deaths with unknown cause. Sixty-two non-AIDS deaths were attributed to non-AIDS cancer and 45 to cardiovascular disease.

TABLE 1. Baseline Characteristics by Background Mortality Group, HIV-CAUSAL Collaboration 2005–2015

	General HIV Population			US Veterans		
Baseline Characteristics	**Included (%)**	**Initiators of ART During Follow-up, %**	**Median (IQR) Follow-up, mo**	**Included (%)**	**Initiators of ART During Follow-up, %**	**Median (IQR) Follow-up, mo**
CD4 count, cells/mm^3						
<100	798 (12)	88	30 (13–54)	532 (20)	87	26 (12–53)
100–200	878 (13)	89	33 (15–57)	435 (16)	87	27 (14–54)
200–349	1725 (25)	85	35 (17–64)	626 (23)	83	29 (14–55)
350–499	1534 (22)	71	34 (15–62)	495 (19)	76	29 (13–60)
≥500	1992 (29)	57	34 (15–62)	584 (22)	60	29 (14–57)
HIV-RNA, copies/mL						
<10,000	1612 (23)	58	35 (15–66)	686 (26)	63	38 (11–53)
10,000–100,000	2855 (41)	75	33 (15–62)	1266 (47)	81	30 (15–58)
>100,000	2460 (36)	85	33 (16–59)	720 (27)	87	27 (12–52)
Sex						
Male	5493 (79)	76	34 (16–63)	2607 (98)	78	28 (13–56)
Female	1434 (21)	70	31 (14–58)	65 (2)	74	30 (15–50)
Mode of acquisition						
Heterosexual	3149 (45)	73	32 (15–59)			
Homo/bisexual	2960 (43)	77	39 (18–69)			
Injection drug use	161 (2)	67	21 (11–45)			
Other/unknown	657 (9)	70	26 (11–50)	2672 (100)	78	28 (13–56)
Geographical origin						
Western Countries	4386 (63)	76	36 (16–66)			
Sub-Saharan Africa	415 (6)	69	26 (11–51)			
Rest of World	611 (9)	72	28 (14–51)			
Unknown country	1515 (22)	73	31 (14–60)	2672 (100) (100R)	74	28 (13–56)
Calendar year						
2005–2009	4212 (61)	77	52 (26–79)	1791 (67)	86	45 (23–67)
2010–2015	2715 (39)	71	19 (11–33)	88 (33)	80	15 (9–22)
Age at enrollment, yr						
50–59	5384 (78)	74	34 (15–63)	1964 (73)	83	29 (13–58)
60–70	1543 (22)	78	34 (15–59)	708 (27)	87	25 (13–48)
HCV coinfection status						
No	5201 (75)	80	35 (17–63)	1555 (58)	81	29 (14–56)
Yes	891 (13)	74	36 (17–72)	1069 (40)	75	28 (13–56)
Unknown	835 (12)	59	22 (11–46)	48 (2)	56	11 (8–18)
All patients	6927	74	34 (15–62)	2672	78	28 (13–56)

HCV, hepatitis C virus; IQR, interquartile range.

Rates of all-cause mortality and non-AIDS mortality per 1000 person-years were 12.3 and 6.3, respectively, for the general HIV population, and 42.4 and 9.7 for US Veterans (Fig. 1). In both populations, the observed rates of all-cause and non-AIDS mortality were higher for males and for individuals with lower CD4 count and older age at baseline.

The estimated 5-year risk of all-cause mortality under immediate ART initiation was 5.3% (95% CI: 4.5 to 6.2) in the general HIV population and 14.4% (12.6–16.7) in the US Veterans (Table 2). The 5-year risk of all-cause mortality was 0.40% (0.10–0.71) lower for the general HIV population and 1.61% (0.79–2.67) lower for US Veterans when comparing immediate initiation vs initiation at CD4 below 350 cells/mm.^{3} The estimated risk of non-AIDS mortality was lower for immediate ART initiation compared with initiation at CD4 <500 and <350 cells/mm^3 in both populations (Table 2). More specifically, the 5-year risk of non-AIDS mortality was 0.17% (−0.07 to 0.43) lower for the general HIV population and 1.0% (0.31–2.0) lower for US Veterans when comparing immediate initiation vs initiation at a CD4 of 350 cells/mm^3. The effect estimates were similar in a sensitivity analysis that classified all unknown-cause deaths as non-AIDS related (Supplemental Digital Content Table 2, http://links.lww.com/QAI/B65). Among individuals in the general HIV population with baseline CD4 count ≥500 cells/mm^3, the estimated risks of all-cause mortality were 2.8% (1.5–4.5) under immediate ART initiation, 3.7% (2.5–4.5) under initiation at CD4 <500 cells/mm^3, and 4.4% (3.1–5.9) under initiation at CD4 <350 cells/mm^3

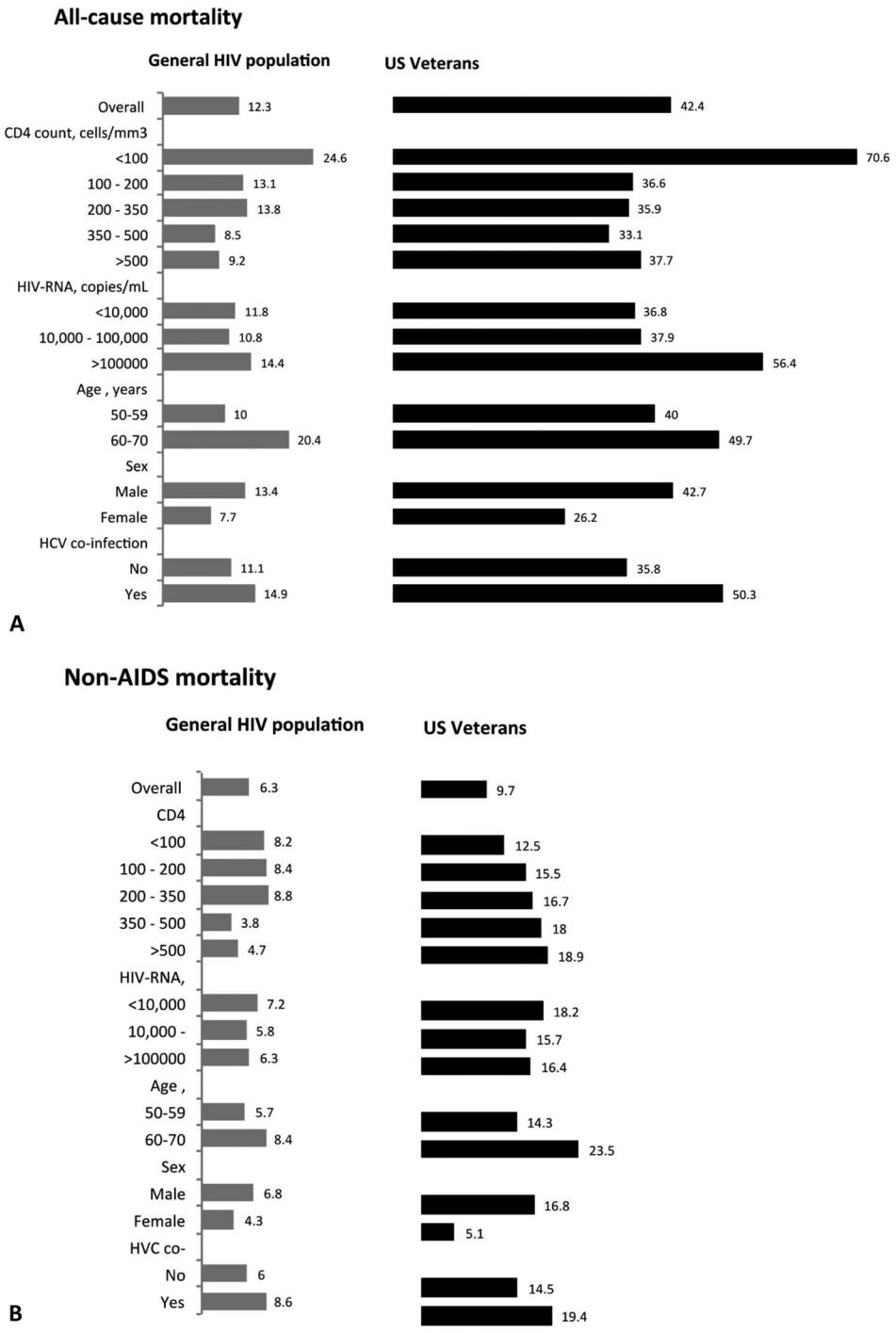

FIGURE 1. Rates (number of events per 1000 person-years) of (A) all-cause mortality and (B) non-AIDS mortality by baseline characteristics and by background mortality group, HIV-CAUSAL Collaboration 2005–2015.

(Table 3). The time-varying means predicted by our models under observed ART initiation were similar to the observed means in the original data (Supplemental Digital Content Figs. 1–3, http://links.lww.com/QAI/B65).

DISCUSSION

We estimated the effect of immediate ART initiation in HIV-positive patients between the ages of 50 and 70 years who were entering routine HIV clinical care. The 5-year risk of all-cause mortality was 0.40% lower for the general HIV population and 1.61% lower for US Veterans when comparing immediate initiation vs initiation at a CD4 count of 350 cells/mm^3. This means that in a hypothetical cohort of 1000 patients, immediate initiation would prevent between 4 and 16 deaths over a 5-year period. The reduction in absolute risk was smaller for non-AIDS mortality. Although small, the estimated benefits of immediate initiation on the all-cause mortality of these older

TABLE 2. Estimated 5-Year Risk of All-Cause Mortality Under 3 ART Initiation Strategies, HIV-CAUSAL Collaboration 2005–2015

		All-Cause Mortality			Non-AIDS Mortality		
Population	**ART Initiation Strategy**	**5-year Risk, % (95% CI)**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**	**5-year Risk, % (95% CI)**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
General HIV population (N = 6927)	Immediate universal	5.3 (4.5 to 6.2)	0 (Ref.)	1 (Ref.)	2.7 (2.1 to 3.4)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	5.5 (4.8 to 6.3)	0.14 (0.04 to 0.28)	1.03 (1.01 to 1.06)	2.8 (2.2 to 3.5)	0.07 (−0.03 to 0.16)	1.03 (0.99 to 1.06)
	<350 cells/mm^3	5.7 (5.1 to 6.6)	0.40 (0.10 to 0.71)	1.07 (1.02 to 1.15)	2.9 (2.3 to 3.7)	0.17 (−0.07 to 0.43)	1.06 (0.97 to 1.16)
US Veterans (N = 2669)	Immediate universal	14.4 (12.6 to 16.7)	0 (Ref.)	1 (Ref.)	6.6 (5.2 to 8.9)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	15.1 (13.3 to 17.4)	0.69 (0.32 to 1.13)	1.05 (1.02 to 1.08)	7.0 (5.6 to 9.2)	0.40 (0.13 to 0.84)	1.06 (1.02 to 1.13)
	<350 cells/mm^3	16.0 (14.5 to 18.4)	1.61 (0.79 to 2.67)	1.11 (1.05 to 1.18)	7.6 (6.4 to 9.9)	1.00 (0.31 to 2.00)	1.15 (1.04 to 1.30)

populations are larger than those estimated among all individuals in the HIV-CAUSAL Collaboration (median age 37 years)[22]: the 7-year risk of all-cause mortality for immediate initiation was only 0.25% (95% CI: 0.40 to 0.37) lower than the risk under initiation at CD4 count <350 cells/mm^3. These findings suggest that in older HIV-positive patients, the benefits of immediate ART initiation on mortality are not offset by age-related comorbidities and potential effects of polypharmacy.

Our findings expand results from randomized controlled trials, such as Temprano and START in which older HIV-positive patients were underrepresented and death events were too few to examine the effect of immediate initiation on mortality.[1,2] Our results are also compatible with those of a subgroup analysis in patients with age ≥50 in START, which showed an increase of 2.24 events of serious diseases per 100 years for deferred vs immediate ART initiation.[23]

Our analysis estimates the risk that would have been observed if all patients in the study, regardless of their CD4 cell count at baseline, had followed each ART initiation strategy. The small magnitude of the benefit of immediate initiation is not surprising as more than half of the included patients had a CD4 cell count <350 cells/mm^3 at baseline. In analyses including only individuals in the general HIV population with CD4 cell count ≥500 cells/mm^3 at baseline, the risk differences were larger: 1.62% for immediate initiation vs initiation with CD4 <350 cells/mm^3. This finding suggests that the benefit of immediate ART initiation in older HIV patients is greater when HIV infection is diagnosed early, which stresses the importance of scaling up testing programs. The high proportion of patients with low CD4 cell count at baseline observed in our data is consistent with reports of late HIV diagnosis among older HIV patients in observational studies and surveillance data.[7,24–27] Lower CD4 cell count at entry into care in older patients can be due to long periods being unaware of their positive HIV status ands faster progression of the HIV disease in patients who become infected at older age.[28–30]

The rates of all-cause and non-AIDS mortality were higher for the US Veterans than for the general HIV population which included individuals in Europe, Canada, and Brazil. The difference in mortality is likely due to a combination of heterogeneity in the data collection protocols and individual characteristics. A contributing factor is the ascertainment of death cases, which has been shown to be more complete in the cohort of US Veterans.[15] In addition to this, in our study, the US Veterans had larger proportions of individuals older than 60 years at study entry and of hepatitis C virus coinfected persons. Also, the US Veterans present substantial morbidity and poor health compared with the general population.[31] However, despite the difference in mortality, our effect estimates were similar in both populations.

Our conclusions indicating the benefits of immediate initiation are compatible with the results from a study using routinely collected data in the United States[32] and extend this study by looking at more recent calendar period, an older age group and non-AIDS mortality. Of note, the observed and estimated 5-year risks under all ART initiation strategies in the

TABLE 3. Estimated 5-Year Risks of All-Cause Mortality Under 3 ART Initiation Strategies for Individuals With CD4 Cell Count ≥500 Cells/mm^3 at Baseline in the General HIV Population, HIV-CAUSAL Collaboration 2005–2015

		All-Cause Mortality		
Population	**ART Initiation Strategy**	**5-year Risk, % (95% CI)**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
General HIV population (N = 2072)	Immediate universal	2.8 (1.6 to 4.4)	0 (Ref.)	1 (Ref.)
	<500 cells/mm^3	3.7 (2.5 to 5.0)	0.86 (0.10 to 1.45)	1.30 (1.03 to 1.72)
	<350 cells/mm^3	4.4 (3.3 to 5.9)	1.62 (0.17 to 2.82)	1.56 (1.05 to 2.41)

general HIV population were lower in our study. The better prognosis demonstrated by our study may be due to the more recent follow-up period (2005–2015 in our study and 1998–2010 in the American study) and a smaller proportion of injecting drug users (2% in our study and 22% in the American study).

Our study has several limitations. First, as in all nonrandomized studies, the validity of our estimates relies on the assumption of no unmeasured confounding. We adjusted for the most important factors used to decide when to initiate ART such as CD4 count, HIV-RNA, and AIDS. However, we did not collect information on age-related comorbidities and concomitant treatments. Had these characteristics influenced the decision to initiate ART in older HIV-positive patients then our estimates could be biased. Second, our methods require that all models are correctly specified. This condition cannot be guaranteed, but it seems plausible because our models resulted in simulated data sets with average outcome and time-varying covariates similar to those in the original data. Third, cause-specific mortality was unknown for a substantial proportion of patients. Therefore, our estimates might underestimate the risk of non-AIDS mortality. As expected, the estimated absolute risks of non-AIDS mortality were higher in the sensitivity analysis assuming that all deaths for unknown cause were non-AIDS deaths, although risk differences and risk ratios were similar. Moreover, it has been shown that the ICD10 classification for cause of death in individuals known to be HIV-positive tends to misclassify liver disease–related mortality into AIDS-related mortality.[33] Finally, the cohorts included in the HIV-CAUSAL Collaboration are not based on random samples of the HIV population, tend to include many HIV seroconverters and might therefore not be fully representative of HIV patients in care in high-income countries. However, this concern is not supported by a recent study showing that individuals enrolled in European cohorts tend to have broadly similar characteristics at HIV diagnosis and the HIV-positive individuals in European Surveillance registries.[34]

In conclusion, immediate initiation of ART seems to be beneficial in reducing all-cause mortality in AIDS-free patients aged 50 years or older, despite their low baseline CD4 count. More effort should be made into diagnosing HIV earlier, particularly in older patients to ensure timely initiation of treatment and follow-up for concomitant comorbidities, thereby maximizing the benefit of early treatment for HIV.

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